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(54) Title: CHOLINESTERASE INHIBITORS FOR SPINAL CORD DISORDERS

(57) Abstract: The invention provides methods for treating and/or preventing spinal cord disorders (e.g., spinal cord ischemia, spinal cord convulsions, spinal cord infarction, spinal cord injury), canine cognitive dysfunctions, and other disorders by administering to a patient in need thereof at least one cholinesterase inhibitor. In one embodiment, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. In other embodiments, the cholinesterase inhibitor can be one or more of phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine, metrifonate, heptastigmine, edrophonium, TAK-147, T-82, and upreazine.



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Cholinesterase Inhibitors for Spinal Cord Disorders

Related Applications

This application claims priority to US Application No. 60/539,982 filed
5 January 30, 2004.

Field of the Invention

The invention provides methods for treating and/or preventing cognitive impairments, dementia, spinal cord injuries and other disorders by administering to a patient a therapeutically effective amount of at least one cholinesterase inhibitor.

Background of the Invention

Cholinesterase inhibitors are described in U.S. Patent No. 4,895,841 and WO 98/39000, the disclosures of which are incorporated by reference herein in their entirety. The cholinesterase inhibitors described in U.S. Patent No. 4,895,841 include donepezil hydrochloride or ARICEPT®, which has proven to be a highly successful
15 drug for the treatment of Alzheimer's disease. There is a need in the art for new and improved treatments for other diseases, disorders, and syndromes that may be characterized by symptoms of spinal cord injuries. The invention is directed to these, as well as other, important ends.

Summary of the Invention

20 The invention provides methods for treating and/or preventing spinal cord ischemia, spinal cord convulsions, spinal cord infarctions, and/or spinal cord injuries by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor.

In another embodiment, the invention provides methods for treating and/or
25 preventing canine cognitive dysfunction (CCD) by administering to a dog in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one cholinesterase inhibitor and at least one compound selected from the group consisting of corticosteroids, anticoagulants, antiepileptics and
30 monoamine oxidase B inhibitors.

In another embodiment, the invention provides a pharmaceutical composition comprising donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof and selegiline or a pharmaceutically acceptable salt thereof.

The invention is described in more detail below.

5

Detailed Description of the Invention

“Patient” refers to animals, preferably mammals, more preferably humans. The term “patient” includes adults and children, and men and women. Children include neonates, infants, and adolescents.

10 The invention provides methods for treating and/or preventing a spinal cord disorder by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. The spinal cord disorder can be any known in the art. Exemplary spinal cord disorders include spinal cord injury, spinal cord ischemia, spinal cord infarction, spinal cord convulsions and the like.

15 In another embodiment, the methods of treating and/or preventing spinal cord disorders comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine
20 oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing spinal cord disorders by administering to a patient in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically
25 acceptable salt thereof.

The invention provides methods for treating and/or preventing a spinal cord injury in a patient in need thereof by administering a therapeutically effective amount of at least one cholinesterase inhibitor. “Spinal Cord Injury” refers to damage to cells within the spinal cord, severing of the nerve tracts that relay signals up and down the
30 spinal cord due to a traumatic event, and/or damage to the spinal cord that results from direct injury to the cord itself, or from indirect injury from damage to the bones, soft tissues, and blood vessels surrounding the spinal cord. Spinal cord injuries can include

contusions (bruising of the spinal cord), compression (caused by pressure on the spinal cord), lacerations (severing or tearing of some nerve fibers), central cord syndrome (damage to the corticospinal tracts of the cervical region of the spinal cord), and paralysis (loss of control over voluntary movement and muscles of the body). The symptoms of spinal cord injury vary somewhat depending on the location of the injury. The symptoms of spinal cord trauma due to cervical (near the neck) injuries can include weakness, paralysis, breathing difficulties (from paralysis of the breathing muscles), spasticity (increased muscle tone), sensory changes, numbness, pain, loss of normal bowel and bladder control, constipation, incontinence, bladder spasms, and abnormal blood pressure. The symptoms of spinal cord injury due to thoracic (chest-level) injuries can include weakness, paralysis, breathing difficulties (from paralysis of the breathing muscles), spasticity (increased muscle tone), sensory changes, numbness, pain, loss of normal bowel and bladder control, constipation, incontinence, bladder spasms, and abnormal blood pressure. Other the symptoms of spinal cord injuries can include pain or sensitivity to stimuli, muscle spasms, sexual dysfunction, bladder infections, lung infections, bedsores, loss of sensation and reflex function below the point of injury, including autonomic activity such as breathing and other activities such as bowel and bladder control.

In another embodiment, the invention provides for methods treating spinal cord injury by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor and at least one corticosteroid. The corticosteroids can be any in the art. Exemplary corticosteroids include methylprednisolone, dexamethasone, and the like. The cholinesterase inhibitor and the corticosteroids can be administered separately or in the form of a composition.

In another embodiment, the methods of treating and/or preventing spinal cord injury comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing spinal

cord injury by administering to a patient in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically acceptable salt thereof.

5 The invention provides methods for treating and/or preventing spinal cord ischemia by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. "Spinal cord ischemia" refers to reduced blood flow to the spinal cord, which is supplied by the anterior spinal artery and the paired posterior spinal arteries. This condition may be associated with
10 arteriosclerosis, trauma, emboli, diseases of the aorta, and other disorders. Prolonged ischemia may lead to infarction of spinal cord tissue. The symptoms of spinal cord ischemia can include dizziness or falling, leg pain brought on by exercise and relieved by rest, impaired gait or legs "giving out," nystagmus (irregular, involuntary movement of the eyes), vomiting, speech impairment, partial, temporary or permanent paralysis of
15 arm, leg and neck muscles on one or both sides, diminished vision, and breathing difficulty.

 In another embodiment, the invention provides for methods treating and/or preventing spinal cord ischemia by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor and at least one
20 anticoagulant. The anticoagulant can be any in the art. Exemplary anticoagulants include warfarin, aspirin, clopidogrel, dipyridamole, and the like. The cholinesterase inhibitor and the anticoagulant can be administered separately or in the form of a composition.

 In another embodiment, the methods of treating and/or preventing spinal cord
25 ischemia comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine
30 oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing spinal cord ischemia by administering to a patient in need thereof a therapeutically effective

amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically acceptable salt thereof.

5 The invention provides methods for treating and/or preventing spinal cord infarction by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. "Spinal cord infarction" refers to a stroke either within the spinal cord or the arteries that supply the spinal cord and is generally caused by the thickening or closing of the major arteries to the spinal cord. The symptoms of spinal cord infarction can include intermittent sharp or burning back
10 pain, aching pain down through the legs, weakness in the legs, paralysis, loss of deep tendon reflexes, loss of pain and temperature sensation, and incontinence.

In another embodiment, the invention provides for methods treating and/or preventing spinal cord infarction by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor and at least one
15 anticoagulant. The anticoagulant can be any in the art. Exemplary anticoagulants include warfarin, aspirin, clopidogrel, dipyridamole, and the like. The cholinesterase inhibitor and the anticoagulant can be administered separately or in the form of a composition.

In another embodiment, the methods of treating and/or preventing spinal cord
20 infarction comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine
25 oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing spinal cord infarction by administering to a patient in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically
30 acceptable salt thereof.

The invention provides methods for treating and/or preventing spinal cord convulsions by administering to a patient in need thereof a therapeutically effective

amount of at least one cholinesterase inhibitor. "Spinal cord convulsions" refers to sudden and often violent motor activity of cerebral or brainstem origin. Convulsions may also occur in the absence of an electrical cerebral discharge. The symptoms of convulsions can include shaking, twitching, staring, or a loss of consciousness.

5 In another embodiment, the invention provides for methods treating spinal cord convulsions by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor and at least one antiepileptic drug. The antiepileptic drug can be any in the art. Exemplary antiepileptic drugs include phenobarbital, phenytoin, carbamazepine, gabapentin, valproate, felbamate, topiramate,
10 zonisamide, primidone, and the like. The cholinesterase inhibitor and the antiepileptic drug can be administered separately or in the form of a composition.

 In another embodiment, the methods of treating and/or preventing spinal cord convulsions comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the
15 monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or
20 preventing spinal cord convulsions by administering to a patient in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically acceptable salt thereof.

 The invention provides methods for treating and/or preventing one or more
25 cognitive impairments caused by a spinal cord disorder (e.g., spinal cord injury, spinal cord ischemia, spinal cord infarction, spinal cord convulsions and the like) by administering to a patient in need thereof at least one cholinesterase inhibitor. "Cognitive impairment" refers to an acquired deficit in one or more of memory function, problem solving, orientation and/or abstraction that impinges on a patient's
30 ability to function independently.

 In another embodiment, the methods of treating and/or preventing one or more cognitive impairments caused by a spinal cord disorder comprise administering a

therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing one or more cognitive impairments caused by a spinal cord disorder by administering to a patient in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically acceptable salt thereof.

The invention provides methods for treating and/or preventing dementia caused by a spinal cord disorder (e.g., spinal cord injury, spinal cord ischemia, spinal cord infarction, spinal cord convulsions, and the like) by administering to a patient in need thereof at least one cholinesterase inhibitor. "Dementia" refers to a global deterioration of intellectual functioning in clear consciousness, and is characterized by one or more symptoms of disorientation, impaired memory, impaired judgment, and/or impaired intellect. The symptoms of "dementia" are generally worse than, and can encompass, the symptoms of "cognitive impairment."

In another embodiment, the methods of treating and/or preventing dementia caused by a spinal cord disorder comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing dementia caused by a spinal cord disorder by administering to a patient in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically acceptable salt thereof.

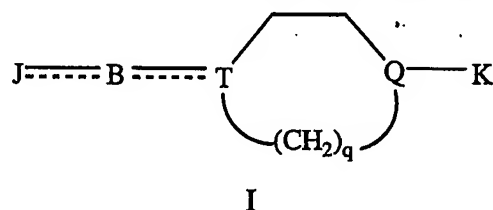
The invention provides methods for treating and/or preventing canine cognitive dysfunction (CCD) by administering to a dog in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. "Canine cognitive dysfunction" is the age related deterioration of cognitive abilities characterized by behavioral changes in dogs that cannot be wholly attributed to general medical conditions such as neoplasia (cancer), infection or organ failure. CCD is caused by physical and chemical changes that affect the brain function in older dogs. CCD is not "normal aging." A number of pathophysiological changes are suspected to play a role in its development, including deposition of amyloid plaques in the cerebral cortex and hippocampal part of the brain, alterations in neurotransmitters, including dopamine, increased levels of monoamine oxidase B (MAOB) in the brain, increased levels of free radicals. The symptoms of CCD include aimless wandering, disorientation, confusion about a previously familiar place, loss of housetraining, forgetting to eat or drink, not responding to previously favorite people, change in sleeping patterns, pacing, forgetting his name, and the like.

In another embodiment, the methods of treating and/or preventing canine cognitive dysfunction comprise administering a therapeutically effective amount of a cholinesterase inhibitor and a monoamine oxidase inhibitor. In one embodiment, the monoamine oxidase inhibitor is a monoamine oxidase B inhibitor. The monoamine oxidase B inhibitor can be any known in the art, such as selegiline, rasagiline, lazabemide, pargyline, mofegiline, and the like. The cholinesterase inhibitor and monoamine oxidase inhibitor can be administered separately or in the form of a composition. In one embodiment, the invention provides methods for treating and/or preventing canine cognitive dysfunction by administering to a dog in need thereof a therapeutically effective amount of donepezil, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof, and a therapeutically effective amount of selegiline or a pharmaceutically acceptable salt thereof.

The cholinesterase inhibitor used in the methods and compositions of the invention can be any in the art. The cholinesterase inhibitor can be, for example, an acetylcholinesterase inhibitor or a butyrylcholinesterase inhibitor. Acetylcholinesterase inhibitors are preferred. Exemplary cholinesterase inhibitors include donepezil, phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline,

velnacrine, huperzine (e.g., huperzine A), metrifonate, heptastigmine, edrophonium, TAK-147 (i.e., 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone fumarate or other salts thereof), T-82, upreazine, and the like. In each of the methods described herein, one or more cholinesterase inhibitors can be used. In one embodiment, one cholinesterase inhibitor is used. In another embodiment, donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof and a second cholinesterase inhibitor are used in the methods or compositions of the invention.

In one embodiment, the cholinesterase inhibitor can be a compound of formula I, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:

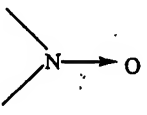


wherein J is

- (a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;
 - (b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9) $C_6H_5-CO-CH(CH_3)-$;
 - (c) a monovalent group derived from a cyclic amide compound;
 - (d) a lower alkyl group; or
 - (e) a group of $R^{21}-CH=CH-$, in which R^{21} is hydrogen or a lower alkoxy carbonyl group;
- B is $-(CHR^{22})_r-$, $-CO-(CHR^{22})_r-$, $-NR^4-(CHR^{22})_r-$, $-CO-NR^5-(CHR^{22})_r-$, $-CH=CH-(CHR^{22})_r-$, $-OCOO-(CHR^{22})_r-$, $-OOC-NH-(CHR^{22})_r-$, $-NH-CO-(CHR^{22})_r-$, $-CH_2-CO-NH-(CHR^{22})_r-$, $-(CH_2)_2-NH-(CHR^{22})_r-$, $-CH(OH)-(CHR^{22})_r-$, $=(CH-CH=CH)_b-$, $=CH-(CH_2)_c-$, $=(CH-CH)_d=$, $-CO-CH=CH-CH_2-$, $-CO-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)-CO-NH-CH_2-$, $-CH=CH=CO-NH-(CH_2)_2-$, $-NH-$, $-O-$, $-S-$, a dialkylaminoalkyl-carbonyl or a lower alkoxy carbonyl;

wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl; R^5 is hydrogen, lower alkyl or phenyl; r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

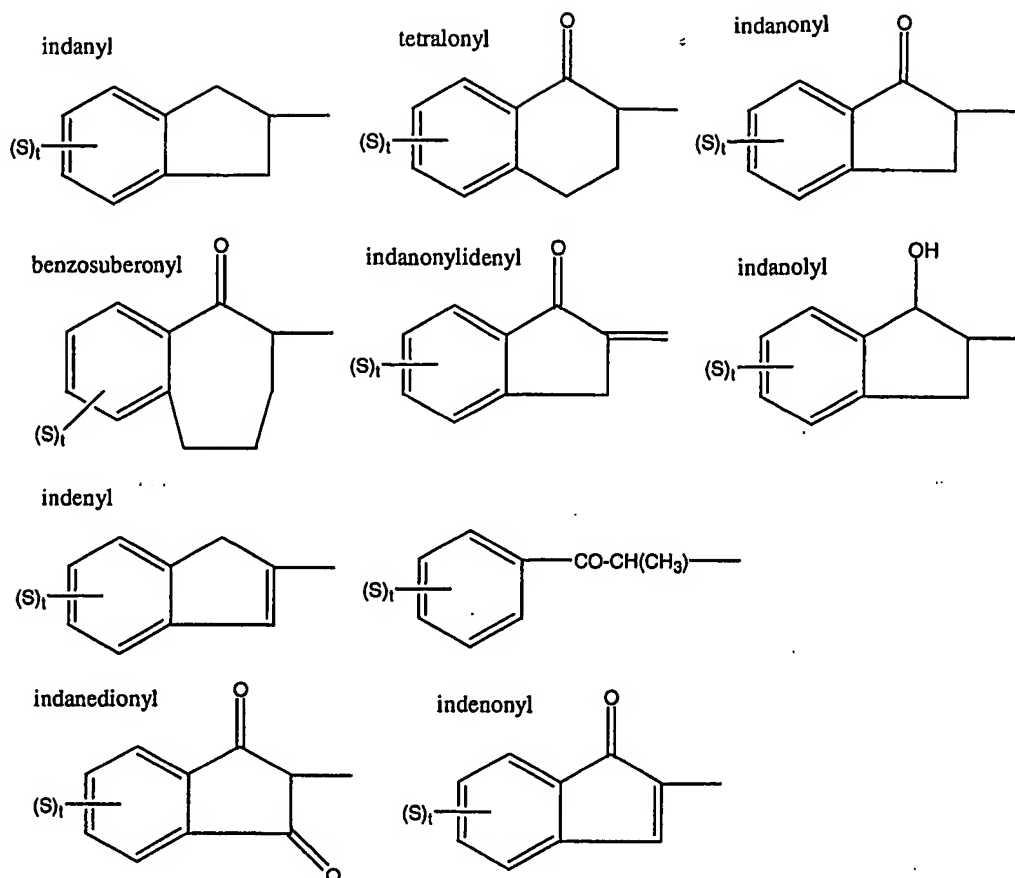
T is nitrogen or carbon;

Q is nitrogen, carbon or  ;

q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxycarbonyl or an acyl; and ----- is a single bond or a double bond.

In the compound of formula I, J is preferably (a) or (b), more preferably (b). In the definition of (b), a monovalent group (2), (3) and (5) and a divalent group (2) are preferred. The group (b) preferably includes, for example, the groups having the formulae shown below:



wherein t is an integer of about 1 to about 4; and each S is independently hydrogen or a substituent, such as a lower alkyl having 1 to 6 carbon atoms or a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferred. The phenyl is most preferred to have 1 to 3 methoxy groups thereon. $(S)_t$ can form methylene dioxy groups or ethylene dioxy groups on two adjacent carbon atoms of the phenyl group. Of the above groups, indanonyl, indanedionyl and indenyl, optionally having substituents on the phenyl, are the most preferred.

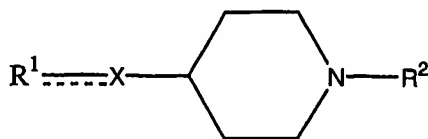
In the definition of B , $-(CHR^{22})_r$, $-\text{CO}-(CHR^{22})_r$, $=(\text{CH}-\text{CH}=\text{CH})_b$, $=\text{CH}-(\text{CH}_2)_c$ and $=(\text{CH}-\text{CH})_d$ are preferable. The group of $-(CHR^{22})_r$ in which R^{22} is hydrogen and r is an integer of 1 to 3, and the group of $=\text{CH}-(\text{CH}_2)_c$ are most preferable. The preferable groups of B can be connected with (b) of J , in particular (b)(2).

The ring containing T and Q in formula I can be 5-, 6- or 7-membered. It is preferred that Q is nitrogen, T is carbon or nitrogen, and q is 2; or that Q is nitrogen, T is carbon, and q is 1 or 3; or that Q is carbon, T is nitrogen and q is 2.

It is preferable that K is a phenyl, arylalkyl, cinnamyl, phenylalkyl or a

phenylalkyl having a substituent(s) on the phenyl.

In another embodiment, the cyclic amine compounds of formula I are the piperidine compounds of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R^1 is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula $R^3\text{-CH=C-}$, where R^3 is a hydrogen atom or a lower alkoxy carbonyl group;

X is $-(\text{CH}_2)_n-$, $-\text{C(O)}-(\text{CH}_2)_n-$, $-\text{N(R}^4)-(\text{CH}_2)_n-$, $-\text{C(O)}-\text{N(R}^5)-(\text{CH}_2)_n-$, $-\text{CH=CH}-(\text{CH}_2)_n-$, $-\text{O-C(O)-O}-(\text{CH}_2)_n-$, $-\text{O-C(O)-NH}-(\text{CH}_2)_n-$, $-\text{CH=CH-CH=CO-}$, $-\text{NH-C(O)}-(\text{CH}_2)_n-$, $-\text{CH}_2-\text{C(O)-NH}-(\text{CH}_2)_n-$, $-(\text{CH}_2)_2-\text{C(O)-NH}-(\text{CH}_2)_n-$, $-\text{CH(OH)}-(\text{CH}_2)_n-$, $-\text{C(O)-CH=CH-CH}_2-$, $-\text{C(O)-CH}_2-\text{CH(OH)-CH}_2-$, $-\text{CH(CH}_3)-\text{C(O)-NH-CH}_2-$, $-\text{CH=CH-C(O)-NH}-(\text{CH}_2)_2-$, a dialkylaminoalkylcarbonyl group, a lower alkoxy carbonyl group;

where n is an integer of 0 to 6; R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R^5 is a hydrogen atom a lower alkyl group or a phenyl group;

R^2 is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

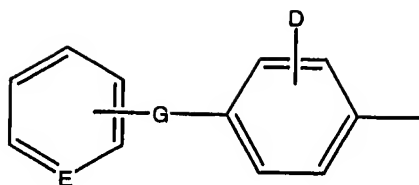
----- is a single bond or a double bond.

The term "lower alkyl group" as used herein means a straight or branched alkyl

group having 1 to 6 carbon atoms. Exemplary "lower alkyl groups" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methyl-pentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-
5 dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethyl-butyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like. The lower alkyl group is preferably methyl, ethyl, propyl or isopropyl; more preferably methyl.

Specific examples of the substituents for the substituted or unsubstituted phenyl;
10 pyridyl, pyrazyl, quinolyl, indanyl, cyclohexyl, quinoxalyl and furyl groups in the definition of R¹ include lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy groups corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms, such as chlorine, fluorine and bromine; a
15 carboxyl group; lower alkoxycarbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group; a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon
20 atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups, such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups, such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups, such as methylcarbonyloxy,
25 ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups, such as a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy lower alkyl groups, such as ethoxymethyl, methoxymethyl and methoxyethyl groups. The "lower alkyl groups" and "lower alkoxy groups" in the above description of the substituent include all the groups derived from the above-mentioned groups. The
30 substituent can be one to three of them, which can be the same or different.

When the substituent is a phenyl group, the following group is within the scope of the substituted phenyl group:



wherein G is -C(O)-, -O-C(O)-, -O-, -CH₂-NH-C(O)-, -CH₂-O-, -CH₂-SO₂-, -CH(OH)-, or -CH₂-S(->O)-; E is a carbon or nitrogen atom; and D is a substituent.

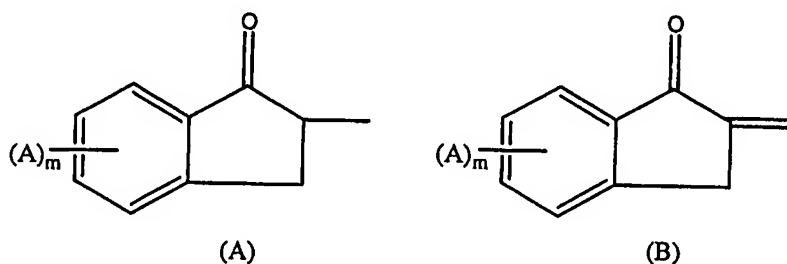
Preferred examples of the substituents (i.e., "D") for the phenyl group include
 5 lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxy carbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzyol and benzylsulfonyl groups. The substituent can be two or more of them, which can be the same or different.

Preferred examples of the substituent for the pyridyl group include lower alkyl
 10 and amino groups and halogen atoms.

Preferred examples of the substituent for the pyrazyl group include lower alkoxy carbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxycarbonyl groups.

With respect to R¹, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group
 15 is preferably a 2-quinolyl or 3-quinolyl group; the quinoxalinyl group is preferably a 2-quinoxalinyl or 3-quinoxalinyl group; and the furyl group is preferably a 2-furyl group.

Specific examples of preferred monovalent or divalent groups derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by formulas (A) and (B):

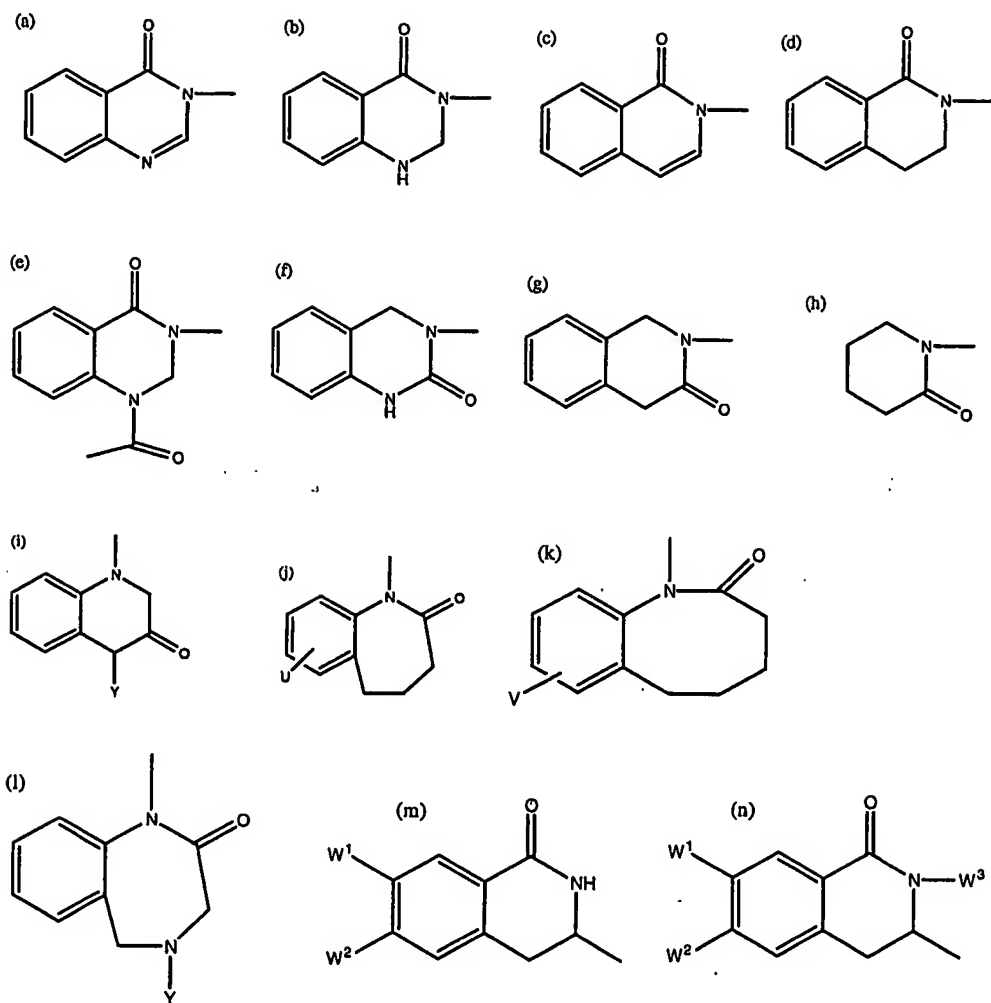


where m is an integer of from 1 to 4, and each A is independently a hydrogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a carboxyl group, a lower alkoxy carbonyl group, an amino group, a lower monoalkylamino group, a lower dialkylamino group, a carbamoyl group, an acylamino
 25 group derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon

atoms, a cycloalkyloxycarbonyl group, a lower alkylaminocarbonyl group, a lower alkylcarbonyloxy group, a halogenated lower alkyl group, a hydroxyl group, a formyl group, or a lower alkoxy lower alkyl group; preferably a hydrogen atom, a lower alkyl group or a lower alkoxy group; most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group can be any one having a cyclic amide group in the structural formula thereof, and is not limited to the above-described specific examples. The cyclic amide group can be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocyclic ring is preferably one formed by condensation with a phenyl ring. In this case, the phenyl ring can be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferred examples of the monovalent group include the following:



In the above formulae, Y is a hydrogen atom or a lower alkyl group; V and U are each a hydrogen atom or a lower alkoxy group (preferably dimethoxy); W¹ and W² are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group; and W³ is a hydrogen atom or a lower alkyl group. The right hand ring in formulae (j) and (l) is a 7-membered ring, while the right hand ring in formula (k) is an 8-membered ring.

The most preferred examples of the above-defined R¹ include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

The most preferred examples of the above-defined X include $-(CH_2)_n-$, an amide group, or groups represented by the above formulae where n is 2. Thus, it is most preferred that any portion of a group represented by the formula $R^1 \text{-----} X \text{-----}$ have a carbonyl or amide group.

The substituents involved in the expressions "a substituted or unsubstituted

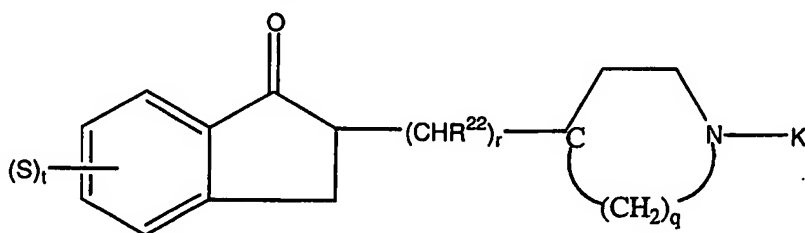
phenyl group” and “a substituted or unsubstituted arylalkyl group” in the above definition of R^2 are the same substituents as those described for the above definitions of a phenyl group, a pyridyl group, a pyrazyl group, a quinolyl group, an indanyl group, a cyclohexyl group, a quinoxalyl group or a furyl group in the definition of R^1 .

5 The term “arylalkyl group” is intended to mean an unsubstituted benzyl or phenethyl group or the like.

Specific examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

Preferred examples of R^2 include benzyl and phenethyl groups. The symbol
 10 $\overline{\text{-----}}$ means a double or single bond. The bond is a double bond only when R^1 is the divalent group (B) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

In another embodiment, the compound of formula II is a compound of formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



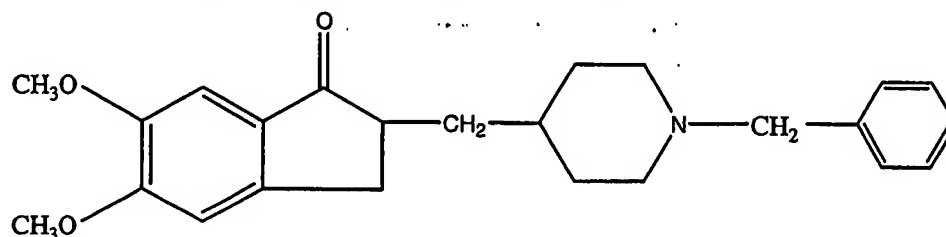
III

wherein r is an integer of about 1 to about 10; each R^{22} is independently hydrogen or methyl; K is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each S is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms; t is an integer of 1 to 4; q is an integer of about 1 to about 3; with the proviso that $(S)_t$ can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

In other embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-

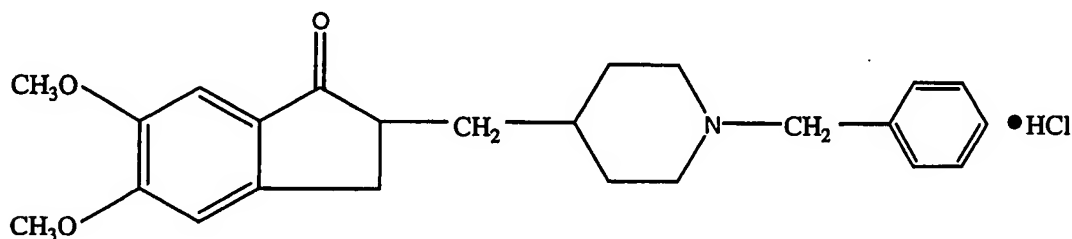
4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; or a stereoisomer and/or a pharmaceutically acceptable salt thereof.

In still other embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, which is represented by formula IV:



IV.

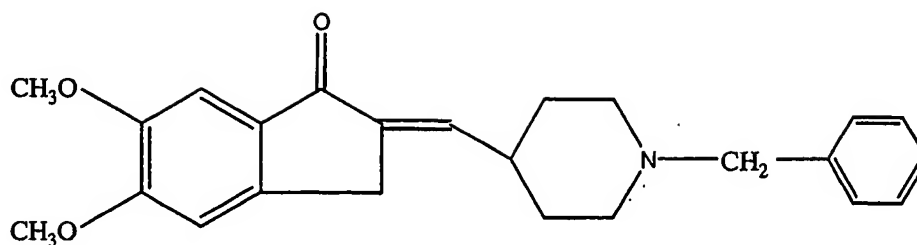
In still other embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride or a stereoisomer thereof, which is also known as donepezil hydrochloride or ARICEPT® (Eisai Inc., Teaneck, NJ), and which is represented by formula IVa:



IVa.

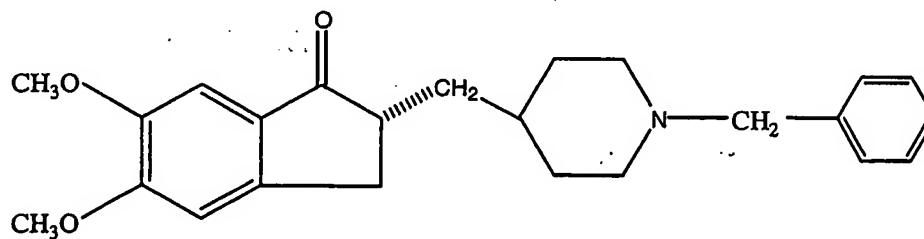
The compounds of the invention can have an asymmetric carbon atom(s), depending upon the substituents, and can have stereoisomers, which are within the scope of the invention. For example, donepezil or pharmaceutically acceptable salts thereof can be in the forms described in Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of which are incorporated by reference herein in their entirety.

Japanese Patent Application No. 4-187674 describes a compound of formula V:



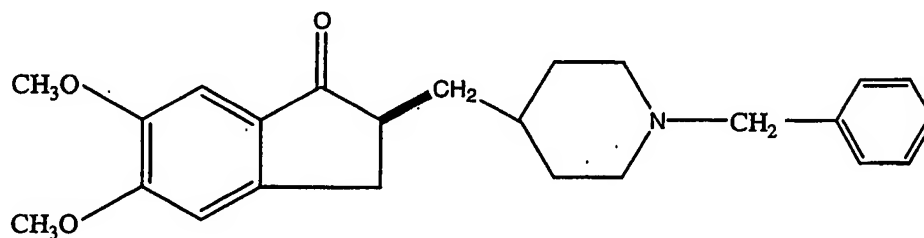
V

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt. Japanese Patent Application No. 4-21670 describes compounds of formula VI:



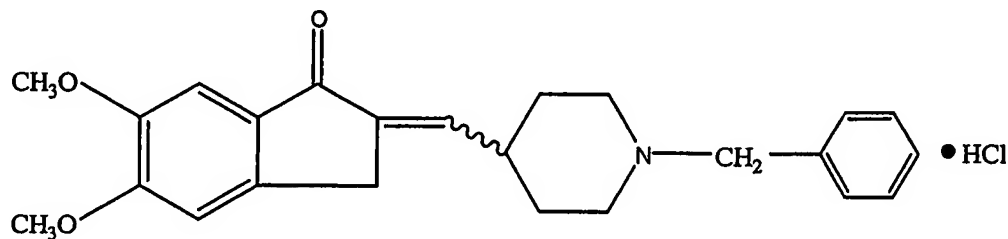
VI

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VII:



VII

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VIII:



VIII.

As described above, the cholinesterase inhibitors and other medications described herein (e.g., corticosteroids, anticoagulants, anti-epileptic drugs, monoamine oxidase inhibitors) can be administered in the form of a pharmaceutically acceptable

salt. Pharmaceutically acceptable salts are well known in the art and include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide and phosphate; and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate. When certain substituents are selected, the compounds of the invention can form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any other pharmaceutically acceptable salt.

The cholinesterase inhibitors can be prepared by processes that are known in the art and described, for example, in U.S. Patent No. 4,895,841, WO 98/39000, and Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of each of which are incorporated by reference herein in their entirety. Donepezil hydrochloride, a preferred cholinesterase inhibitor for use in the methods described herein, is commercially available as ARICEPT® from Eisai Inc., Teaneck, NJ. The other medications described herein (e.g., corticosteroids, anticoagulants, anti-epileptic drugs, monoamine oxidase inhibitors) are commercially available, are in development, and/or can be prepared by processes described in the literature. For example, selegiline is commercially available from Teva Pharmaceuticals Ltd. The cholinesterase inhibitors and other medications described herein can be administered as pharmaceutical combinations. A pharmaceutical combination is a pharmaceutical formulation comprising both active ingredients or separate pharmaceutical dosage forms.

The dosage regimen for treating and preventing the diseases described herein with the cholinesterase inhibitors and other medications can be selected in accordance with a variety of factors, including the age, weight, sex, and medical condition of the patient, the severity of the migraines, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the drugs, whether a drug delivery system is used and whether the cholinesterase inhibitor is administered as part of a drug combination.

When more than one cholinesterase inhibitor is administered to a patient and/or when the cholinesterase inhibitor(s) is administered in conjunction with another

medication, the compounds can be separately administered about the same time as part of an overall treatment regimen, i.e., as a drug cocktail or combination therapy. "About the same time" includes administering the compounds at the same time, at different times on the same day, or on different days, as long as they are administered as part of
5 an overall treatment regimen.

The cholinesterase inhibitors can be administered to treat or prevent the diseases described herein in doses of about 0.01 milligrams to about 300 milligrams per day, preferably about 1 milligram to about 50 milligrams per day, more preferably about 1 milligram to about 20 milligrams per day. The doses can be administered in one to
10 four portions over the course of a day, preferably once a day. One skilled in the art will recognize that when the cholinesterase inhibitors are administered to human children or dogs, the dose can be smaller than the dose administered to human adults, and that the dose can be dependent upon the size and weight of the patient (e.g., human child or dog). A human child or dog can be administered the cholinesterase inhibitors in doses
15 of about 0.01 milligrams to about 15 milligrams per day; about 0.1 milligrams to about 12 milligrams per day; about 0.5 milligrams to about 10 milligrams per day; about 1 milligram to about 5 milligrams per day; or about more preferably about 1 milligram to about 3 milligrams per day.

In other embodiments of the methods described herein, donepezil
20 hydrochloride, which is commercially available as ARICEPT® (Eisai Inc., Teaneck, NJ), can be administered as tablets containing either 5 milligrams donepezil hydrochloride or 10 milligrams donepezil hydrochloride. The tablets can be administered one to about four times a day. In preferred embodiments, one 5 milligram or one 10 milligram ARICEPT® tablet is administered once a day for the methods
25 described herein. One skilled in the art will appreciate that when donepezil hydrochloride is administered to human children or dogs, the dose can be smaller than the dose that is administered to human adults.

The cholinesterase inhibitors and other medications of the invention can be administered orally, topically, parenterally, by inhalation (nasal or oral), or rectally in
30 dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral includes subcutaneous, intravenous, intramuscular, intrathecal, intrasternal injection, or infusion techniques.

Preferably, the cholinesterase inhibitors are orally administered as tablets. When administered to children, the cholinesterase inhibitors are preferably orally administered in a liquid dosage form. When administered to dogs, the cholinesterase inhibitors are administered with a veterinarily acceptable carrier.

5 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, of the cholinesterase inhibitors can be formulated according to the art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxyethylene sorbitan monolaurate and the like), pH
10 modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like) and preservatives. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol.
15 Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil can be used including synthetic mono- or diglycerides, in addition, fatty acids, such as oleic acid, can be used in the preparation of injectables. The preparations can
20 be lyophilized by methods known in the art.

 In one embodiment, the cholinesterase inhibitors of the invention can be administered to the patient by a spinal pump (e.g., spinal fluid injector pump). In a spinal pump, the medication is administered (e.g., infused, injected) to the patient's spinal cord area. For example, the medication can be administered into the intrathecal
25 space around the spinal cord. Spinal pumps are known in the art and described for example, in U.S. Patent No. 6,682,508, the disclosure of which is incorporated by reference herein in its entirety.

 Solid dosage forms for oral administration of the cholinesterase inhibitors can include chewing gum, capsules, tablets, sublingual tablets, powders, granules, and gels;
30 preferably tablets. In such solid dosage forms, the active compound can be admixed with one or more inert diluents such as lactose or starch. As is normal practice, such dosage forms can also comprise other substances including lubricating agents such as

magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents. The tablets can be prepared with enteric or film coatings, preferably film coatings. For administration to dogs, the tablets can be flavored (e.g., beef, cheese, bacon) so that the tablet is palatable to the dog.

5 Sublingual administration refers to the administration of the cholinesterase inhibitors in the mouth (e.g., under the tongue, between the cheek and gum, between the tongue and roof of the mouth). The highly vascular mucosal lining in the mouth is a convenient location for the cholinesterase inhibitors to be administered into the body. To make tablets, the cholinesterase inhibitors can be admixed with pharmaceutically
10 acceptable carriers known in the art such as, for example, vehicles (e.g., lactose, white sugar, mannitol, glucose, starches, calcium carbonate, crystalline cellulose, silicic acid, and the like), binders (e.g., water, ethanol, myranol, glucose solution, starch solution, gelatin solution, polyvinylpyrrolidone, and the like), disintegrators (e.g., dry starch, sodium, alginate, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene
15 sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, and the like), absorption promoters (e.g., quaternary ammonium base, sodium laurylsulfate, and the like), wetting agents (e.g. glycerin, starches, and the like), lubricants (e.g., stearates, polyethylene glycol, and the like), and flavoring agents (e.g., sweeteners). The tablets can be in the form of a conventional tablet, a molded tablet, a
20 wafer and the like.

In other embodiments, the solid dosage form can be packaged as granules or a powder in a pharmaceutically acceptable carrier, where the granules or powder are removed from the packaging and sprinkled on food or mixed with a liquid, such as water or juice. In this embodiment, the cholinesterase inhibitors can be mixed with
25 flavoring or sweetening agents. The packaging material can be plastic, coated paper, or any material that prevents water or moisture from reaching the granules and/or powder.

Liquid dosage forms for oral administration of the cholinesterase inhibitors can include pharmaceutically acceptable emulsions, solutions, sublingual solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as
30 water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents. To make sublingual solutions, the cholinesterase inhibitors can be admixed with

various carriers, excipients, pH adjusters, and the like (e.g., water, sugar, lactic acid, acetic acid, fructose, glucose, saccharin, polyethylene glycol, propylene glycol, alcohol, bentonite, tragacanth, gelatin, alginates, aspartame, sorbitol, methylparaben, propylparaben, sodium benzoate, artificial flavoring and coloring agents).

5 For administration by inhalation, the cholinesterase inhibitors can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by inhalation, the cholinesterase inhibitors can be administered in the form of a dry powder composition or in the form of a liquid spray.

10 Suppositories for rectal administration of the cholinesterase inhibitors can be prepared by mixing the active compounds with suitable nonirritating excipients such as cocoa butter and polyethylene glycols that are solid at room temperature and liquid at body temperature. Alternatively, an enema can be prepared by for rectal administration of the cholinesterase inhibitors.

15 For topical administration to the epidermis, the cholinesterase inhibitors can be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The cholinesterase inhibitors can also be administered via iontophoresis or osmotic pump. Ointments, creams and lotions can be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Alternatively,
20 ointments, creams and lotions can be formulated with an aqueous or oily base and can also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the cholinesterase inhibitors can be mixed to form a smooth, homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2%
25 (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such topically administrable compositions can contain polyethylene glycol 400. To form ointments, the cholinesterase inhibitors can be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II) (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene
30 glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the transdermally administrable compositions for topical application.

The cholinesterase inhibitors can also be topically applied using a transdermal

system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the cholinesterase inhibitors and laminated to an impermeable backing. For example, the cholinesterase inhibitors can be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches can include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

The invention provides for the cholinesterase inhibitors to be administered nasally to a patient to treat the diseases and disorders described herein and those described, for example, in PCT/US02/29734, WO 01/66114, and U.S. Patent Nos. 6,482,838, 6,458,807 and 6,455,544, the disclosures of which are incorporated by reference herein in their entirety. "Administered nasally" or "nasal administration" is intended to mean that at least one cholinesterase inhibitor is combined with a suitable delivery system for absorption across the nasal mucosa of a patient, preferably a human. Generally, lower doses of the cholinesterase inhibitor can be used for nasal administration when compared, for example, to the dose required for the oral administration of the cholinesterase inhibitor.

The cholinesterase inhibitors of the invention can be administered, for example, as nasal sprays, nasal drops, nasal suspensions, nasal gels, nasal ointments, nasal creams or nasal powders. The cholinesterase inhibitors can also be administered using nasal tampons or nasal sponges. The cholinesterase inhibitors of the invention can be brought into a viscous basis via systems conventionally used, for example, natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the compositions, many other excipients known in the art can be added such as water, preservatives, surfactants, solvents, adhesives, antioxidants, buffers, bio-adhesives, viscosity enhancing agents and agents to adjust the pH and the osmolarity.

The nasal delivery systems can take various forms including aqueous solutions, non-aqueous solutions and combinations thereof. Aqueous solutions include, for example, aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous solutions
5 include, for example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

In other embodiments, the nasal delivery system can be a powder formulation. Powder formulations include, for example, powder mixtures, powder microspheres,
10 coated powder microspheres, liposomal dispersions and combinations thereof. Preferably, the powder formulation is powder microspheres. The powder microspheres are preferably formed from various polysaccharides and celluloses selected from starch, methylcellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, carborner, alginate polyvinyl alcohol, acacia, chitosans, and mixtures of two or more
15 thereof.

In certain embodiments, the particle size of the droplets of the aqueous and/or non-aqueous solution or of the powders delivered to the nasal mucosa can be, for example, about 0.1 micron to about 100 microns; from about 1 micron to about 70 microns; from about 5 microns to about 50 microns; or from about 10 microns to about
20 20 microns. The particle sizes can be obtained using suitable containers or metering devices known in the art. Exemplary devices include mechanical pumps in which delivery is made by movement of a piston; compressed air mechanisms in which delivery is made by hand pumping air into the container; compressed gas (e.g., nitrogen) techniques in which delivery is made by the controlled release of a
25 compressed gas in the sealed container; liquefied propellant techniques in which a low boiling liquid hydrocarbon (e.g., butane) is vaporized to exert a pressure and force the composition through the metered valve; and the like. Powders may be administered, for example, in such a manner that they are placed in a capsule that is then set in an inhalation or insufflation device. A needle is penetrated through the capsule to make
30 pores at the top and the bottom of the capsule and air is sent to blow out the powder particles. Powder formulation can also be administered in a jet-spray of an inert gas or suspended in liquid organic fluids.

In one embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one cholinesterase inhibitor dispersed in a nasal delivery system that improves the solubility of the cholinesterase inhibitor. The nasal delivery system that improves solubility can include one of the following or combinations thereof: (i) a glycol derivative (e.g., propylene glycol, polyethylene glycol, mixtures thereof); (ii) a sugar alcohol (e.g., mannitol, xylitol, mixtures thereof); (iii) glycerin; (iv) a glycol derivative (e.g., propylene glycol, polyethylene glycol or mixtures thereof) and glycerin; (v) ascorbic acid and water; (vi) sodium ascorbate and water; or (vii) sodium metabisulfite and water.

10 In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one cholinesterase inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the cholinesterase inhibitor, at least one pharmaceutically acceptable thickening agent and at least one humectant. The nasal delivery system can optionally
15 further comprise surfactants, preservatives, antioxidants, bio-adhesives, pH adjusting agents, isotonicity agents, solubilizing agents, and/or other pharmaceutically acceptable excipients. The cholinesterase inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In another embodiment, the invention provides a nasally administrable
20 pharmaceutical composition comprising at least one cholinesterase inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one solubilizing agent, at least one pharmaceutically acceptable thickening agent and at least one humectant. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, surfactants, preservatives, antioxidants, bio-
25 adhesives, and/or other pharmaceutically acceptable excipients. The cholinesterase inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one cholinesterase inhibitor and a nasal
30 delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the cholinesterase inhibitor, at least one pharmaceutically acceptable thickening agent, at least one humectant, and at least one surfactant. The nasal delivery

system can optionally further comprise pH adjusting agents, isotonicity agents, solubilizing agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The cholinesterase inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

5 In yet another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one cholinesterase inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one pharmaceutically acceptable thickening agent, at least one humectant, at least one surfactant, and at least one solubilizing agent. The nasal delivery system can optionally
10 further comprise buffers, pH adjusting agents, isotonicity agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The cholinesterase inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

 In yet another embodiment, the invention provides a nasally administrable
15 pharmaceutical composition comprising at least one cholinesterase inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the cholinesterase inhibitor, at least one pharmaceutically acceptable thickening agent, at least one humectant, at least one surfactant, and at least one solubilizing agent. The nasal delivery system can optionally further comprise buffers,
20 pH adjusting agents, isotonicity agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The cholinesterase inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

 The nasally administrable pharmaceutical compositions of the invention preferably provide a peak plasma concentration of the cholinesterase inhibitor in less
25 than one hour, preferably within about 5 minutes to about 30 minutes, more preferably within about 5 minutes to about 20 minutes, after administration to the patient.

 The buffer has a pH that is selected to optimize the absorption of the cholinesterase inhibitor across the nasal mucosa. The particular pH of the buffer can vary depending upon the particular nasal delivery formulation as well as the specific
30 cholinesterase inhibitor selected. Buffers that are suitable for use in the invention include acetate (e.g., sodium acetate), citrate (e.g., sodium citrate dihydrate), phthalate, borate, prolamine, trolamine, carbonate, phosphate (e.g., monopotassium phosphate,

disodium phosphate), and mixtures of two or more thereof.

The pH of the compositions should be maintained from about 3.0 to about 10.0. Compositions having a pH of less than about 3.0 or greater than about 10.0 can increase the risk of irritating the nasal mucosa of the patient. Further, it is preferable that the pH of the compositions be maintained from about 3.0 to about 9.0. With respect to the non-aqueous nasal formulations, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa.

The solubilizing agent for use in the compositions of the invention can be any known in the art, such as carboxylic acids and salts thereof. Exemplary carboxylic acid salts include acetate, gluconate, ascorbate, citrate, fumarate, lactate, tartrate, maleate, maleate, succinate, or mixtures of two or more thereof.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. For example, the viscosity may be at least 1000 cps; from about 1000 to about 10,000 cps; from about 2000 cps to about 6500 cps; or from about 2500 cps to about 5000 cps. Thickening agents that can be used in accordance with the present invention include, for example, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans, and mixtures of two or more thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation.

The nasally administrable compositions can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used include, for example, sorbitol, mineral oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and mixtures of two or more thereof. The concentration of the humectant will vary depending upon the agent selected. In one embodiment, the humectant can be present in the nasal delivery system in a concentration ranging from about 0.01% to about 20% by weight of the composition.

In other embodiments, the nasal delivery system can further comprise surfactants which enhance the absorption of the cholinesterase inhibitor. Suitable surfactants include non-ionic, anionic and cationic surfactants. Exemplary surfactants

include oleic acid, polyoxyethylene derivatives of fatty acids, partial esters of sorbitol anhydride, such as for example, Tweens (e.g., Tween 80, Tween 40, Tween 20), Spans (e.g., Span 40, Span 80, Span 20), polyoxyl 40 stearate, polyoxy ethylene 50 stearate, fusieates, bile salts, octoxynol, and mixtures of two or more thereof. Exemplary
5 anionic surfactants include salts of long chain hydrocarbons (e.g., C₆₋₃₀ or C₁₀₋₂₀) having one or more of the following functional groups: carboxylates; sulfonates; and sulfates. Salts of long chain hydrocarbons having sulfate functional groups are preferred, such as sodium cetostearyl sulfate, sodium dodecyl sulfate and sodium tetradecyl sulfate. One particularly preferred anionic surfactant is sodium lauryl sulfate
10 (i.e., sodium dodecyl sulfate). The surfactants can be present in an amount from about 0.001% to about 50% by weight, or from about 0.001% to about 20% by weight.

The pharmaceutical compositions of the invention may further comprise an isotonicity agent, such as sodium chloride, dextrose, boric acid, sodium tartrate or other inorganic or organic solutes.

15 The nasal pharmaceutical compositions of the invention can optionally be used in combination with a pH adjusting agent. Exemplary pH adjusting agents include sulfuric acid, sodium hydroxide, hydrochloric acid, and the like.

To extend shelf life, preservatives can be added to the nasally administrable compositions. Suitable preservatives that can be used include benzyl alcohol, parabens,
20 thimerosal, chlorobutanol, benzalkonium chloride, or mixtures of two or more thereof. Preferably benzalkonium chloride is used. Typically, the preservative will be present in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

25 Other ingredients which extend shelf life can be added such as for example, antioxidants. Some examples of antioxidants include sodium metabisulfite, potassium metabisulfite, ascorbyl palmitate and the like. Typically, the antioxidant will be present in the compositions in a concentration of from about 0.001% up to about 5% by weight of the total composition.

30 Other optional ingredients can also be incorporated into the nasal delivery system provided that they do not interfere with the action of the cholinesterase inhibitor or significantly decrease the absorption of the cholinesterase inhibitor across the nasal

mucosa.

The nasal delivery systems can be made following the processes described in, for example, U.S. Patent Nos. 6,451,848, 6,436,950, and 5,874,450, and WO 00/00199, the disclosures of which are incorporated by reference herein in their entirety.

5 Each of the patents, patent applications, and publications cited herein are incorporated by reference herein in their entirety.

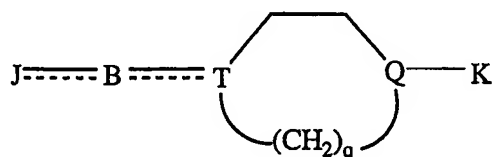
It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.

10

Claims

What is claimed is:

1. A method for treating a spinal cord disorder in a patient in need thereof comprising administering a therapeutically effective amount of at least one cholinesterase inhibitor to treat the spinal cord disorder.
2. The method of claim 1, wherein the spinal cord disorder is a spinal cord injury, spinal cord ischemia, a spinal cord infarction or a spinal cord convulsion.
3. The method of claim 1, wherein the cholinesterase inhibitor is donepezil, a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof.
4. The method of claim 1, wherein the cholinesterase inhibitor is donepezil, pheneserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine, metrifonate, heptastigmine, edrophonium, 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-8-yl)-1-propanone, T-82, or upreazine.
5. The method of claim 1, further comprising administering a therapeutically effective amount of at least one compound selected from the group consisting of an anticoagulant, an anti-epileptic, a corticosteroid and a monoamine oxidase B inhibitor.
6. The method of claim 5, wherein the monoamine oxidase B inhibitor is selegiline, rasagiline, lazabemide, pargyline, or mofegiline.
7. The method of claim 6, wherein the monoamine oxidase B inhibitor is selegiline.
8. A method for treating a spinal cord disorder in a patient in need thereof comprising administering a therapeutically effective amount of a compound of formula (I), a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



I

wherein J is (a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and

(7) furyl; (b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9)

$\text{C}_6\text{H}_5\text{—CO—CH}(\text{CH}_3)\text{—}$; (c) a monovalent group derived from a cyclic amide

5 compound; (d) a lower alkyl group; or (e) a group of $\text{R}^{21}\text{—CH=CH—}$, in which R^{21} is hydrogen or a lower alkoxy carbonyl group;

B is $-(\text{CHR}^{22})_r$, $-\text{CO}-(\text{CHR}^{22})_r$, $-\text{NR}^4-(\text{CHR}^{22})_r$, $-\text{CO-NR}^5-(\text{CHR}^{22})_r$,
 $-\text{CH=CH}-(\text{CHR}^{22})_r$, $-\text{OCOO}-(\text{CHR}^{22})_r$, $-\text{OOC-NH}-(\text{CHR}^{22})_r$, $-\text{NH-CO}-(\text{CHR}^{22})_r$,
 $-\text{CH}_2\text{-CO-NH}-(\text{CHR}^{22})_r$, $-(\text{CH}_2)_2\text{-NH}-(\text{CHR}^{22})_r$, $-\text{CH}(\text{OH})-(\text{CHR}^{22})_r$,
 10 $=(\text{CH-CH=CH})_b$, $=\text{CH}-(\text{CH}_2)_c$, $=(\text{CH-CH})_d$, $-\text{CO-CH=CH-CH}_2-$,
 $-\text{CO-CH}_2\text{-CH}(\text{OH})\text{-CH}_2-$, $-\text{CH}(\text{CH}_3)\text{-CO-NH-CH}_2-$, $-\text{CH=CH=CO-NH}-(\text{CH}_2)_2-$, $-\text{NH-}$,
 $-\text{O-}$, $-\text{S-}$, a dialkylaminoalkyl-carbonyl or a lower alkoxy carbonyl;

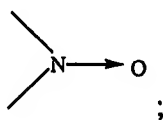
wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl; R^5 is hydrogen, lower alkyl or phenyl;

15 r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

20

Q is nitrogen, carbon or



q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxy carbonyl or an acyl; and

25

----- is a single bond or a double bond.

9. The method of claim 8, wherein the spinal cord disorder is a spinal cord injury, spinal cord ischemia, a spinal cord infarction or a spinal cord convulsion.

10. The method of claim 8, wherein the compound of formula (I) is donepezil, a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof.

30

11. The method of claim 8, further comprising administering a

therapeutically effective amount of at least one compound selected from the group consisting of an anticoagulant, an anti-epileptic, a corticosteroid and a monoamine oxidase B inhibitor.

12. The method of claim 11, wherein the monoamine oxidase B inhibitor is
5 selegiline, rasagiline, lazabemide, pargyline, or mofegiline.

13. The method of claim 12, wherein the monoamine oxidase B inhibitor is selegiline.

14. A method for treating canine cognitive dysfunction in a dog in need
thereof comprising administering a therapeutically effective amount of at least one
10 cholinesterase inhibitor.

15. The method of claim 8, wherein the cholinesterase inhibitor is donepezil, a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of at least one cholinesterase inhibitor and at least one compound selected from
15 the group consisting of an anticoagulant, an anti-epileptic, a corticosteroid and a monoamine oxidase B inhibitor.

17. The pharmaceutical composition of claim 14, wherein the cholinesterase inhibitor is donepezil, a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof.

18. The pharmaceutical composition of claim 14, wherein the cholinesterase inhibitor is donepezil, phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine, metrifonate, heptastigmine, edrophonium, 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1*H*-1-
25 benzazepin-8-yl)-1-propanone, T-82, or upreazine.

19. The pharmaceutical composition of claim 14, wherein the monoamine oxidase B inhibitor is selegiline, rasagiline, lazabemide, pargyline, or mofegiline.

20. The pharmaceutical composition of claim 17, wherein the monoamine oxidase B inhibitor is selegiline.

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